UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,669	11/01/2001	Robert H. Broyles	OKL010-107/00727A	5327

32425 7590 11/03/2004

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,669	BROYLES ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,19,22 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *11 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19,22,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/17/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 19, 2004 has been entered.

In the amendment and response filed 5/17/04, Claims 1, 19, 22, 24, 25, and 27 have been amended, and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 5/17/04 response would be addressed to the extent that they apply to current rejection.

Sequence Compliance

It is noted that the amendment and response are not fully responsive to the Office action mailed 1/14/04 because applicants fail to address the requirement for sequence compliance.

The computer readable form of sequence listing submitted 10/20/03 was technically flawed, thus, could not be entered into the PTO database. A full response to

this Office action must include a new CRF Sequence Listing and a statement that the content of the paper and CRF copies are the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19, 22, 24, 25, and 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and following. The arguments presented in the 5/17/04 response would be addressed in the order they presented as subtitled by the applicants in the Remarks.

A. Evidence of intracellular Expression is *relevant* to enablement.

Applicants first asserted that the examiner has dismissed out of hand the evidence of record regarding the expression of ferritin-H using genetic transformation, and argued that providing ferritin-H in any form will impact beta-globin production.

In response, the Office has repeatedly acknowledged the *in vitro* findings based on nucleic acid transformation experiments disclosed both in the prior art of record (e.g. *Picard et al*) and in the instant specification (e.g. page 9, paper #16), which shows the relevance of the subject matter. However, it is well known in the art, that protein therapy and nucleic acid gene therapy are two distinct fields of scientific study, and such is reflected in the patent classification system. The two therapeutic methods are patentably distinct because a protein and a nucleic acid are structurally different

chemical compounds, have distinct physical and chemical properties, different modes of operation, and pharmacokinetics when administered *in vivo*. A prior art disclosing a method of using a protein for treating a disease is generally not applied to reject claims to a method of treating the same disease with a nucleic acid expressing the same protein, because when evaluating the enablement of the later method, distinct technical consideration is required.

For the record, there is no dispute over the ***relevance*** of the experimental data obtained from the *in vitro* nucleic acid transformation study, the nucleic acid study contributed to the understanding of the ferritin-H function, and how it influences beta-globin production. The question is whether this is ***sufficient*** as the *sole* support for the enablement of the claimed *in vivo* protein therapy of the sickle cell disease. The claimed process being a therapeutic means of using ferritin-H protein, the standard for evaluation is whether the ferritin-H could be efficiently delivered (exposed) to the nucleus of the globin-producing cells in a significant amount into significant population of cells, and whether such delivery would lead to suppressing sickle cell disease and correction of the disease phenotype. This standard requires considerations beyond the molecular mechanism of ferritin-H function, it requires considerations from the ferritin-H delivery to its physiological and pharmacological behavior, and it requires the consideration of overall and long-term consequence of the exogenous ferritin-H being in the nuclei of globin-producing cells and in the context of the pathogenesis of sickle cell disease. It is based on the state of the art, the knowledge of the skilled in the art, and the art-known hurdles for *in vivo* protein therapy and the clinical state in the therapy of

sickle cell diseases, that the disclosure is questioned for its adequacy of providing enablement.

With respect to the delivery of ferritin-H in its native form as a protein, and its possible pharmacological behavior, since the art of record is completely silent and the specification only prophetically contemplates such, the Office can only look for what is known in the art generally for ferritin-H and protein nucleus delivery. According to *Harrison et al* (Bioch Biophy Acta 1996;1275:161-203, IDS), ferritin molecule as a whole have 24 protein subunits arranged in 432 symmetry to give a hollow shell with an 80Å diameter cavity capable of storing up to 4500 Fe(III) atoms as an inorganic complex. Ferritin molecules isolated from vertebrates are composed of two types of subunit heavy chain (H) and light chain (L), which are folded as 4-helix bundles each having a fifth short helix at roughly 60^0 to the bundle. Here, we are facing delivering a relatively large protein molecule with complicated three-dimensional structure crossing through cell membrane, cytoplasmic membrane, and into nucleus of the globin-producing cells. Is this feasible? The newly submitted publications by *Myron-Holtz et al* teach that exogenous ferritin molecule as a whole can be taken up by receptors on the surface of erythroid precursor cells. This brings the whole ferritin molecule through the cell membrane, however, the publication does not teach whether the H chain ferritin, not in the form of a whole complex, could be taken up by the receptor, since the ligand-receptor interaction often depends on the three-dimensional structures on both. Further, *Myron-Holtz et al* also teach that internalized ferritins stayed in the endosome and being degraded by a proteolytic process to release its iron. These exogenous ferritins did not

even reach cytoplasm let alone nucleus before being degraded. With respect to the effect of ferritin-H in the cell nuclei, the evidence on record is all publications delivered a nucleic acid encoding and expressing ferritin-H (e.g. *Picard et al, Broyles et al*). This fact by itself may be an indication that it is difficult for whatever reason to deliver a ferritin-H protein efficiently into the nucleus of the cell where the ferritin-H functions, so that nucleic acid is used as the alternative. Of course, it is entirely possible to deliver a macromolecule protein cross the plasma membrane and into the nucleus of a cell, although not without difficulty. For example, *Schwarze et al* (Trends Cell Biol 2000 July; 10:290) teach three protein-transduction domains (PTDs) that could be linked to a desired peptide for delivery to all tissues. Although it is unknown whether ferritin-H is suitable for PTD-mediated delivery, at the least, this means could be further explored. Interestingly, at the end, *Schwarze et al* concluded, "ALTHOUGH UNRESTRICTED ACCESS OF PROTEINS INTO CELLS IS NOW POSSIBLE, WE HAVE A POOR GRASP OF HOW THIS TECHNOLOGY WORKS. BASED ON THE WHOLE-ANIMAL STUDIES, ALL CELLS APPEAR TO BE SUSCEPTIBLE TO PROTEIN TRANSDUCTION. AT THE MOLECULAR LEVEL, IT IS UNCLEAR HOW PROTEINS BEHAVE WHEN INTERACTING WITH THE CELL MEMBRANE OR IF ANY PARTICULAR MOLECULE IS NECESSARY TO MEDIATE ENTRY" (last section, page 294). Such teaching illustrated the state of the art at the time of instant priority date, that protein delivery into cells is still underdevelopment and highly unpredictable. Yet, this may be the least barrier, there are more issues beyond the intracellular delivery. *Schwarze et al* go on to teach, "FROM THE LIMITED DATA CURRENTLY AVAILABLE, TRANSDUCTION ACROSS THE CELLULAR MEMBRANE IS THOUGHT TO RESULT IN A PARTIAL OR COMPLETE UNFOLDING OF THE PROTEIN THAT WILL PROBABLY DIFFER FROM ONE PROTEIN TO ANOTHER. THEREFORE, ONCE INSIDE THE CELL, THE TRANSDUCED PROTEIN REQUIRES

REFOLDING TO OBTAIN BIOLOGICALLY ACTIVE PROTEIN" (last section, page 294), and concluded, "CURRENTLY, THERE ARE ONLY A HANDFUL OF PAPERS IN THE LITERATURE THAT DESCRIBE THE SUCCESSFUL TRANSDUCTION OF FULL-LENGTH PROTEINS AND REPORT A PHENOTYPE. WE THINK THAT IN VITRO, REFOLDING IS CURRENTLY THE RATE-LIMITING STEP, AND NOT TRANSDUCTION, WHEREAS IN VIVO ANIMAL MODELS NEED IMPROVEMENTS IN BOTH AREAS" (last paragraph, page 295, all emphasis added). Additionally, "BASIC PHARMACOLOGICAL QUESTIONS OF TISSUE DISTRIBUTION, PROTEIN HALF-LIFE, IMMUNOGENICITY AND MODES OF DELIVERY ARE ALSO IMPORTANT QUESTIONS THAT NEED TO BE ADDRESSED IN A QUANTITATIVE FASHION" (paragraph bridging pages 294-5). For example, *Schwarze et al* teach, "AN EFFECTIVE DRUG MUST BE ACTIVE ONLY IN THE DISEASED CELL". Since the art of record (e.g. Harrison et al) teaches that Ferritin is ubiquitously distributed in many different types of cells and living species, not limited to the globin-producing cells, it is important to deliver it selectively. The specification only contemplates using a ligand to selectively deliver ferritin-H, but the specification fails to teach any ligand specific for globin-producing cells. Assuming the ligand is well known in the art, the specification fails to teach the mode of operation of purposed ligand-ferritin-H complex, how the ligand would affect the cell and nucleus entry, the unfolding and refolding processes, and the function of the refolded ferritin-H. The specification fails to address any one of the questions as discussed by the skilled artisans, thus, in light of the state of the art and coupled with the instant disclosure, it is reasonable to conclude that the specification fails to provide an enabling disclosure to support the claimed invention.

Moreover, assuming the intracellular delivery of ferritin-H are not an issue, *Buckel* (Trends Pharmacol Sci 1996;17:450-6), while acknowledges the great

advantage of using natural proteins for therapy, teaches, "THE PROBLEM IS, HOWEVER, THAT PROTEINS HAVE TO BE ADMINISEED FROM OUTSIDE THE BODY FOR THERAPEUTIC PURPOSES. TO THIS EXTENT, THEY ARE AT A CONSIDERABLE DISADVANTAGE COMPARED TO THE SMALLER CHEMICAL DRUGS. UNLIKE THE LATTER, PROTEINS CANNOT YET BE ADMINISTERED ORALLY AND USUALLY HAVE TO BE INJECTED. BUT EVEN THEN PROBLEMS CAN ARISE WITH THE NATURAL POTENCY OF PROTEINS. EXOGENOUS ADMINISTRATION RESULTS IN VARYING DRUG CONCENTRATIONS THAT CAN DEVIATE GREATLY FROM THE NATURAL SITUATION. SYSTEMIC ADMINISTRATION MIGHT EVEN DETRACT FROM LOCAL EFFECTIVENESS, FOR EXAMPLE IN THE INTERATION OF CELLS OF THE IMMUNE SYSTEM" (right column, page 454). Thus, besides cell specificity, nucleus targeting, protein pharmacokinetics, host immune response would be another concern for ferritin-H therapy because the nature of the sickle cell disease determines that such protein therapy is a long-term one.

Assuming none of the above is an issue for ferritin-H therapy, the diverse functions of ferritin-H determines that it is unknown and unpredictable the long-term consequence results from the presence of therapeutically effective amount of exogenous ferritin-H in the cell nuclei, the overall function of the globin-producing cells in the context of the sickle cell disease. To this end, *Buckel* teaches parameters that influence the probability of biological or chemical substances being successfully developed into medicinal products: "(1) COMPLEXITY OF THE TARGET TO BE INHIBITED OR ACTIVATED; (2) INTRACELLULAR OR EXTRACELLULAR TARGET; (3) NUMBER OF MOLECULES REQUIRED; AND (4) CHRONIC OR ACUTE DISEASE SITUATION" (paragraph bridging pages 455-6). Hence, it is important to look at the nature of the sickle cell diseases, the underlying

mechanism of pathogenesis, the treatment strategy, and the complexity of the target that ferritin-H affects.

Sickle cell disease results from a point mutation in the beta-globin gene that leads to substitution of a polar glutamate residue at codon 6 with a hydrophobic valine residue. In homozygous disease, erythrocytes form bizarre sickle shapes caused by polymerization of deoxygenated hemoglobin containing the mutant β-globin. Such erythocytes have reduced flexibility and occlusion in small capillaries. Currently, the treatment strategy is to supply natural antisickling hemoglobins such as fetal hemoglobin (gamma-globin) and normal beta-globin to correct the diseased polymerization and prevent sickle cell formation. The instant specification teaches that the *nuclear* ferritin-H has a gene regulatory function in human cells, it binds to a specific DNA sequence centrally placed in the promoter of adult β-globin gene and represses transcription of this gene in transfected cells. In working examples, the specification teaches that the ferritin-H represses the transcriptional activity of β-globin promoter in a transient co-transfection assay with plasmid vectors expressing ferritin and reporter gene, wherein the expression level of a reporter β-CAT was repressed by over 60% in cultivated CV-1 cells in the presence of an expression clone of human ferritin-H (Specification, Section bridging pages 40-41). The specification prophetically concludes, "Thus, a ferritin-H gene or peptide targeted to the correct cells offers a cure for sickle cell disease in which the β-globin gene is mutated, as well as other genetic diseases where there is mismanagement of iron" (Specification, page 23, 1st paragraph). Applicants now proposed a new treatment strategy, i.e. suppress the production of the

mutant beta-globin using the gene repressor ferritin-H. This strategy requires an excessive amount of ferritin-H (over-expression) in the nuclei of globin-producing cells. Since we do not know the actual consequence of administering ferritin-H in these cells, we can look at the consequence of overexpression of ferritin-H, which is acknowledged by the applicant as *relevant*. *Picard et al* teach overexpression of ferritin H subunit in cultured erythroid cells (globin-producing cells) results in a reduced accumulation of β-globin mRNA, which is desired for the proposed strategy. However, overexpression of ferritin H also leads to impaired hemoglobin synthesis, and greatly suppressed ferritin-L subunit production (abstract). What is the consequence of impaired hemoglobin synthesis? Worsened anemia? We do not really know. What is the consequence of suppressed ferritin-L subunit? Theoretically, it would suppress the normal structure and function of the ferritin in general since H-chains are important for Fe(II) oxidation and L-chains assist in core formation of the three dimensional structure. More importantly, what is the consequence of long-term suppression of beta-globin? The specification is silent with this aspect. However it is noteworthy there is a type of beta-chain hemoglobinopathy named beta-thalassemia, which arises from the total or partial reduction in synthesis of structurally normal beta-globin chain. Lack of beta-globin synthesis results in precipitation of free alpha-globin chains and the subsequent destruction of erythroid precursors in the bone marrow and spleen (see e.g. *Herzog et al*, Expert Rev Cardiovascular Ther 2003;1:215-32). Thus, theoretically, long-term administration of exogenous ferritin-H may lead to another disease, beta-thalassemia.

Considering the numerous barriers taught in the above cited art of record, it is not surprising that *Mankad* (Pediatric Pathol Mol Med 2001;20:1-13) teaches, at a post-filing date, that the molecular lesion in the hemoglobin and the abnormality in the beta globin gene were identified more than fifty years ago. It was hoped that a "cure" or a "satisfactory treatment" would soon follow. However, although decades of research improved our understanding of the pathophysiology of sickle cell disease, the treatment strategy is still under development, multiple treatment regimen targeting different stages and mechanisms of the disease development is required, and yet to become a reality (See particularly the first section of the article). Apparently, even at the post-filing date, ferritin-H has not yet entered the picture as a potential or well accepted therapeutic strategy. Thus, it is incumbent upon applicants to provide an enabling disclosure for what is now claimed. The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

It is noted that in the second paragraph of the Remarks in page 5, applicants mentioned additional data from the inventors' laboratory. However, such data have not

been properly identified, thus the Office could not evaluate the addition data. Applicants are reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). MPEP 716.01(c).

Applicants then acknowledged even with the additional data from the inventors' laboratory, nothing specifically provide evidence on protein administration. This point has been repeatedly indicated in the previous Office actions, that the specification or the post-filing publication fail to provide any evidence *in vitro or in vivo* for the premise of administering an exogenous ferritin-H chain to the nucleus of a cell and achieve a therapeutic effect. Although this alone would not fail the test of enablement, when coupled with the knowledge of the skilled and the state of the art, the question concerning the enablement or lack thereof would be reasonably raised.

Applicants then concluded that "the data of record, though in vitro in nature, provide a strong indication that ferritin-H can act to alter the expression of b-globin genes". In response, the applicants fail to provide any data of record neither *in vitro* nor *in vivo* in the field of protein therapy; thus, it fails to provide an enabling disclosure for the claimed subject matter in light of the state of the art.

Since there is no working example specifically addresses ferritin-H protein therapy, the following teachings of the M.P.E.P. apply. "THE TEST OF ENABLEMENT IS WHETHER ONE REASONABLY SKILLED IN THE ART COULD MAKE OR USE THE INVENTION FROM THE DISCLOSURES IN THE PATENT COUPLED WITH INFORMATION KNOWN IN THE ART WITHOUT UNDUE EXPERIMENTATION." (UNITED STATES V. TELECTRONICS, INC., 857 F.2D 778, 785, 8 USPQ2D 1217, 1223 (FED. CIR. 1988)). "DETERMINING ENABLEMENT IS A QUESTION OF LAW BASED ON

UNDERLYING FACTUAL FINDINGS". IN RE VAECK, 947 F.2D 488, 495, 20 USPQ2D 1438, 1444 (FED. CIR.1991); ATLAS POWDER CO. V. E.I. DU PONT DE NEMOURS & CO., 750 F.2D 1569, 1576, 224 USPQ 409, 413 (FED. CIR. 1984). One aspect of such factual findings to be considered is "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING. THE "PREDICTABILITY OR LACK THEREOF" IN THE ART REFERS TO THE ABILITY OF ONE SKILLED IN THE ART TO EXTRAPOLATE THE DISCLOSED OR KNOWN RESULTS TO THE CLAIMED INVENTION. IF ONE SKILLED IN THE ART CAN READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THE CLAIMED INVENTION PERTAINS, THEN THERE IS PREDICTABILITY IN THE ART. ON THE OTHER HAND, IF ONE SKILLED IN THE ART CANNOT READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THAT CLAIMED INVENTION PERTAINS, THEN THERE IS LACK OF PREDICTABILITY IN THE ART. ACCORDINGLY, WHAT IS KNOWN IN THE ART PROVIDES EVIDENCE AS TO THE QUESTION OF PREDICTABILITY. (MPEP 2164.02, 03). The Office relied on the combined teachings of the prior- and post-filing date art to provide a reasonable basis to conclude that one skill in the art could not practice the invention without undue experimentation. "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03)

In light of the discussion *supra*, the only reasonable conclusion is that the instant disclosure fails to meet the statutory enablement requirement set forth under this provision even though it provides relevant information.

B. Differences between ex vivo and in vivo claims.

Applicants argue that claim 25 is limited to ex vivo embodiments, and thus any arguments regarding the additional difficulties of in vivo therapies are not applicable against this claim.

In response, as discussed *supra*, the barriers for developing ferritin-H to a drug to treat sickle cell disease requires far more considerations than just protein-cell contacting, which should be much easier to accomplish *ex vivo*. Further, although the cell-protein contacting may not be an issue *ex vivo*, the nucleus delivery of the ferritin-H is at issue. Further, assuming the ferritin-H could be properly delivered to the nucleus of a target cell, and the transcriptional activity of beta-globin promoter could be repressed and would not influence the overall function of globin-producing cells *in vivo*, the half-life of a protein is short, the specification fails to teach upon cell transplantation, whether the ferritin-H will stay in the nucleus, and the repression could last long enough so that the disease phenotype could be corrected by the cell implant. It is the questions of kind that the office concluded that the specification fails to provide an enabling disclosure for all pending claims including claim 25.

Applicants then cited *In re Brana* and alleged that the examiner is posing an incorrect question improperly require clinical effective data for supporting enablement of the claimed invention. In response, it is noted that *In re Brana* case law discusses whether a claimed *compound* has the asserted utility to be used *in vivo*, not a *method* claiming treatment effect in humans. It is also noted that the Office did not require a

clinical trial to support the claimed method, but questions the correlations of *in vitro* transient nucleic acid transformation data with respect to the claimed subject matter drawn to *in vivo* protein therapy that deemed to be a long term one; and questions whether the claimed method is fully enabled based on the teachings of those skilled in the art as discussed above. This is appropriate because 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

Applicants then cited *In re Marzocchi* and accused that the examiner offered no explanation as to why those of skill in the art would not expect to achieve a clinical benefit. In response, the explanations have been offered in pages 9 through 13 of paper #16, and pages 4-7 of the Office action mailed 1/14/04, reviewing the state of art concerning therapy for sickle cell disease before and after the instant filing date and compared such to the guidance provided in the specification, raising issues such as art known hurdles in protein therapy and protein nucleus delivery as taught by the skilled artisan, e.g. *Buckel*, and pointing to the disconnection between basic molecular research and clinical therapy such as taught by *Mankad et al.* Since it appears the applicant was not satisfied with the explanation, further discussion has been offered by the Office as set forth under § A of this action. Applicants are reminded that *In re Marzocchi* teaches "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT

FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC".

C. The only remaining question is one of protein delivery.

The 5/17/04 response started this argument with "applicants have shown in a variety of ways that increasing ferrtin-H levels in cell nuclei reduces b globin transcription". This is an inaccurate statement. Applicants have shown in one way, and one way only, that increasing ferritin-H levels in cell nuclei reduces β globin transcription by a transient co-transfection assay in cultured cells, i.e. the expression level of β-CAT (a β-globin promoter-driven reporter gene) stimulated by EKLF was repressed by 60% by co-transfection of an expression clone of human H-chain ferritin (Specification, Section bridging pages 40-41).

Then applicants submitted publications to indicate that ferritin when applied exogenously to cells with appropriate receptors can be internalized and taken up into cell nuclei. Applicants particularly discussed the experiment taught by *Myron-Holtz et al*, which showed that human erythroid precursors grown in culture possess membrane receptors that bind and internalize acid isoferritin. Indeed, *Myron-Holtz et al* teach that developing human erythroid cells possess on their surface, receptors that bind specifically and internalize acid isoferritin, they also shown that exogenous acid ferritin were rapidly internalized by the cells and were degraded by proteolysis in a lysosome-like acidic cellular compartment and released its iron by a proteolytic process.

Here, two problems arise. First, the ferritin was internalized as a whole complex having both the H- and L-chains with or without irons in an acid three-dimensional form, it is not clear whether ferritin-H is acidic, and when not in such a 3-D form it would interact with the surface receptor of developing erythroid cells so it can be efficiently internalized. Second, the ferritin only reached endosomal compartment, and were quickly degraded by proteases, they did not reach the cytoplasma or nucleus where the function is performed for the intended use of this invention. *Leimberg et al* cited the teaching of *Myron-Holtz et al.* Accordingly, the submitted references could not support the intracellular or nucleus delivery of ferritin-H.

Moreover, in view of the discussion under section A of this Office action, there are more barriers for achieving therapeutic effects of ferritin-H on sickle cell diseases. Thus, protein delivery is apparently not the only remaining question.

D. Expert Declarations

Applicants submitted two declarations of Dr. McDonald and Dr. Lin. The contents of the declarations are substantially the same beyond the personal credentials, thus, would be addressed together.

Section 2 acknowledged the general findings of the applicants.

Section 3 acknowledged the implications of the inventor's finding in the treatment of beta-globin-related diseases, such as sickle cell anemia, and concluded, "thus, using ferritin-H as a therapeutic agent for treating sickle cell anemia is a logical extension of Dr. Broyles's work. In response, applicants are reminded that the standard for

evaluating the enablement is not whether the discovery could be logically extended in the future, the criteria for enablement is the claimed subject matter has been fully enabled "at the time the application was filed". As stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocol is not disclosed in the specification indicates that the specification does not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention. The court has held, "[U]NLESS AND UNTIL A PROCESS IS REFINED AND DEVELOPED TO THIS POINT-WHERE SPECIFIC BENEFIT EXISTS IN CURRENTLY AVAILABLE FORM-THERE IS INSUFFICIENT JUSTIFICATION FOR PERMITTING AN APPLICANT TO ENGROSS WHAT MAY PROVE TO BE A BROAD FIELD. . . . A PATENT IS NOT A HUNTING LICENSE. . . .[I]T IS NOT A REWARD FOR THE SEARCH, BUT COMPENSATION FOR ITS SUCCESSFUL CONCLUSION".

It is noted that Doctors stated that human cells, which take up exogenous ferritin-H, also transport it to the cell nucleus by an active transport mechanism. Since such important fact is missing in the instant disclosure, the Office could not evaluate whether such knowledge is available at the filing of the instant application, and how the ferritin-H survived the degradation of proteases as indicated in the newly submitted publications discussed in section C, and the efficiency of such active transport relative to a therapeutic effect. Hence the enablement to this portion of the disclosure could not be determined.

Section 4 speaks the feasibility of this approach, the doctors, based on the history of protein drugs and exemplified by human insulin and C-GSF, concluded that given what is known about the uptake and transport of ferritin-H, this protein is a promising candidate for treating indications such as sickle cell disease. In response, again, the standard set forth in MPEP for evaluation is not whether a given chemical is promising for developing to a drug, the standard is whether the disclosure has established that the chemical is a drug, i.e. contributed to alleviate or cure a disease at the time of the filing of the patent application. Again, the court (*Brenner v. Manson*, 148 USPQ 689, 696 (US SupCt., 1966)) held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion" (Emphasis added).

With regards to protein drugs, it should be made clear that each protein has its distinct physical and biological property, distinct tissue and cell specificity, and distinct target. Further, each deals with different diseases having different pathogenesis and treatment strategy. As *Buckel* puts it, the complexity of the target to be inhibited or activated, intracellular or extracellular target, number of molecules required, and chronic or acute disease situation, these just a few of points which contribute to making a promising chemical into a drug a complex one. For example, the insulin and GM-CSM

target surface receptors., For these proteins, delivery to blood stream may be sufficient for their function, whereas the ferritin-H needs to function in nuclei of globin-producing and non-globin producing cells concerning the claimed subject matter. Hundreds and thousands of in vitro and in vivo studies have been performed before Insulin and GM-CSF being used in clinical treatment. Yet, not even one study has been published or disclosed by the applicant, *in vitro or in vivo* for the attempt to characterize the delivery of ferritin-H peptide, and cellular phenotypic effects of such delivery. Thus when coupled with the state of the art and the knowledge of the skilled in the art, it appears to be premature to conclude administrating ferritin-H polypeptide would suppress sickle cell disease.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* administration to cell nuclei at therapeutic levels, in particular for the treatment of sickle cell diseases, the lack of direction or guidance in the specification as well as the absence of working examples with regard to therapeutic regimens, and the breadth of the claims directed to the delivery of ferritin-H peptide, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of Claims 1, 19, 27 are re-instated under 35 U.S.C. 102(b) as being anticipated by *Adams et al* (New Eng J Med 1998;39:5-11), and as evidenced by *Atkinson et al* (Biochem Cell Biol 1989;67:52-7, IDS) and *Sowemimo-Coker* (Transfus Med Rev 2002 Jan;16:46-60).

The claims are drawn to a method for suppressing sickle cell disease, comprising introducing exogenous ferritin-H or derivative thereof into globin-producing cells. *Adams et al* teach preventing a first stroke of sickle cell anemia in children by Red blood transfusion (See particularly abstract and § Methods). Although not relied upon, *Atkinson et al* teach that ferritins are present in red blood cells, and will be released upon lysis of RBC, and *Sowemimo-Coker* teaches that the lysis of RBC (hemolysis) does occur during processing, storage and transport (abstract). Thus, the nuclear ferritin-H is present in RBC transfusion unit. Because the claims are broadly drawn to any means of exposing exogenous ferritin-H to globin-producing cells, the red blood transfusion is encompassed by the claims. Thus, *Adams et al* anticipate instant claims.

In the response filed 10/30/03, applicant's counsel argued the cited reference does not disclose the present invention because blood donations are only taken from adults, and adult blood does not contain ferritin-H.

Upon further review of prior art of record and consideration, it is noted that there is no clear evidence on record that the above statement is supported. In fact, in the post-filing publication of Broyles et al, the inventor states "ferritins from human liver (rich in L chains) and heart (rich in H chains)..." (paragraph bridging pages 9145). It appears

that there is a difference in the richness of ferritin-H for different tissue or cells, but it is not a total lacking in adults, and it is unlikely that ferritin-H would be missing from adult red blood cells since it plays such an important role in carrying irons. Further clarification with factual evidence is needed to overcome this rejection. Applicants are reminded that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). MPEP 716.01(c).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

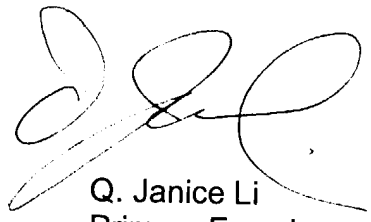
Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Q. Janice Li
Primary Examiner
Art Unit 1632

QL
November 1, 2004